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(54) Title: TISSUE AUGMENTATION

(57) Abstract

The present invention relates to use of a biologically degradable polymer for manufacturing of a composition for treating an impaired tissue by injecting said composition into said tissue for the purpose of joining and/or augmenting the same, said composition being in liquid state at the time of injection and in solid state following injection.

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Tissue Augmentation.

The present invention relates to tissue augmentation. More precisely the invention relates to use of a biologically degradable polymer for injection into a tissue for the purpose of joining and/or augmenting the same.

Most commonly, formed cracks or impaired tissue are not treated at all but there exists some surgical methods for treating said defectives. However, these surgical methods are time consuming and not always effective. Therefore, there is a large need for rapid and effective treatment in view of the great number of patients suffering from the above conditions. A common example is tissue impairement due to decreased function of the sphincter muscle of the intestine or urether.

It is previously known to treat impaired tissue with material being expected to remain in the patients body for the rest of the patients life following incorporation thereof. Examples of such material are polymethacrylate, Teflon paste and apatite. However, the effect obtained with these materials is only filling and not tissue joining or augmenting. The same applies for the biologically degradable material collagen and glucose amino glucans previously also being used for treating impaired tissue.

In WO 91/01126 a floating membrane of biologically degradable material is described which hardens in situ following injection into dental tooth pockets. This material is used for tissue regeneration and cannot be used for tissue augmentation as it comprises pores in the range 3-500 μm, enabling cells etc. to pass through the membrane and thereby growing together with surrounding tissues.

The present invention provides tissue augmentation by a new use of known polymer materials. The polymer materials being used according to the invention are biocompatible and are well known within the medical field. These materials can be made injectable and their nature is such that they remain at the site where they have been applied by injection. In this context the difference

between filling out tissue and augmenting tissue must be emphasized. According to the invention the polymer is injected into the tissue and when it has hardened it becomes a network controlled by the injection. This network joins the tissue desired to be augmented. With other words, this creates an active augmentation with a number of augmenting points in the tissue. During the healing process, this netword also exerts a certain degree of irritation, with the augmenting material disappearing and being replaced with connective tissue.

The polymer being used in the composition of the invention can be polyglycolides and copolymerisates thereof, polylactides and copolymerisates thereof, poly-β-hydroxybutyrate and copolymerisates thereof, poly-p-dioxanon, poly-δ-valerolactone, poly-ϵ-caprolactone, methylmethacrylate-N-vinyl pyrrolidone copolymerisate, polyesther amides, polyesthers of oxanoic acid, polydihydropyranes, poly-alcyl-2-cyanoacrylates, polyurethanes, polyvinylalcohol, polypeptides, poly-β-malic acid, poly-β-alcanoic acids and alginates of different forms. It is also possible to use a combination of one or more of these polymers. The amount of the polymer depends on the molecular weight of the polymer. For a high molecular weight polymer, a low concentration is satisfactory, and vice versa.

The above polymers for use in the present composition, are in a liquid form at the time of applying by injection and in solid or semi solid form following injection into the tissue desired to be augmentented. Preferably, the polymer is dissolved in a solvent, such as acetone, prior to the injection into the tissue. Prior to injection, it is also possible to heat the polymer to < 42°C, which is the maximal temperature tolerated by the tissue. When alginates in liquid forms are used these are crosslinked in the tissue by 2-valent ions.

According to another embodiment of the invention, the composition is also provided with a drug, such as, for example, growth promoting agents and antibiotics.

Furthermore, the composition can optionally be provided with monofilament, e.g. small pieces of vicrylsuture to increase the reinforcing effect of the polymer network.

Yet another embodiment of the invention is to comprise already known filling or expanding material, such as collagen, glucose amino glucans etc., in the composition according to the invention. Especially preferred filling materials are those forming a gas in aqueous environment at about 37°C, such as particulate citric acid and sodium bicarbonate. The amount thereof determines the degree of sweeling of the composition in vivo following injection thereof and gives "spongy" or porous properties to the composition. Another preferred expanding material is dextranomer particles giving the injected composition porous properties. The amount of dextranomer particles is choosen to enable modulation of the composition following injection.

The method of tissue augmentation according to the invention can be described according to the following:

1. A cannula or other suitable instrument is inserted into the tissue where the augmentation is desired.
2. By the instrument, which can be cutting or blunt, cavities are created in the tissue.
3. The instrument is withdrawn.
4. A cannula or catheter filled with liquid a composition comprising a polymer material is inserted in the cavity (-ies), and thereafter the composition is injected therein.
5. The cannula is withdrawn and the composition is allowed to harden.

The invention will now be described more closely below in relation to some examples.

Example 1:

Joining of a menisc

A crack in a menisc can be joined according to the invention in the following way:

A sharp, cutting needle is, under atropic guidance, inserted in the crack so that this is penetrated, and thereafter the needle is withdrawn. A mass comprising 30% polylactide in acetone reinforced with 2 mm pieces of monofilament vicrylsuture is inserted in the crack by a catheter provided with a cannula. The mass is injected so that a lump is formed in the beginning and end of the crack and the cannula is slowly withdrawn. During the first 5 to 10 minutes after the application the crack is pressed together with a blunt instrument, e.g. the sleeve of the needle catheter.

Example 2:

Reflux correcting

A common defective of children of up to 10 years of age is incomplete function of the inlet of the urether into the urine bladder. The normal back valve function has been lost and urine is flowing back from the bladder to the urether. Therefore, these children often have urether infections with accompanied threatened kidney function. To protect the kidneys, these children often need antibiotics for years. If this does not help, surgery is performed. It is a costly and relatively complicated operation with long term healing and great discomfort for the patient.

On the basis that the defective has its origin in a tissue impairement of the bladder wall, a tissue augmentation was performed with cystoscopic technique by inserting a needle in the wall of the bladder beneath the mucous membrane.

This tissue augmentation was performed by injecting about 1 ml 20% polymer lactide solution under the mucous membrane of the bladder. Following hardening of the solution, the formed disc exerted good resistance against the inner pressure of the bladder preventing back leakage. The lactide polymer is now degraded (6 months after injection) and leaves a connective tissue providing sufficient resistance for a remained back valve function.

Example 3:

Augmentation of sphincter function

The body is provided with shut off mechanisms of sphincter type in above all the gastro-intestinal tract and in the urethra of the urine bladder. As the abdomen is exposed to overpressure in connection with body exercise or sneezing/coughing, these openings have to be shut effectively. Therefore, the pylorus has a "ring muscle" which rapidly and effectively can shut off the contents of the stomach. Also the lower part of the stomach is closed with a ring muscle so that food can be portioned in the intestine in a controlled way. Finally, the last part of the intestine has a double sphincter to securely hold faeces under control. In all of these cases, and in more not disclosed cases, the ring closing function can partly be lost or impaired forming a leakage. This is very embarassing and a great problem for many patients. On the other hand, the conditions are not life threatening and often associated with high age and therefore the hospitals give no priority to this cause. A simplified method would undoubtedly be very welcome for patients as well as physicians.

In a majority of sphincter function disturbances there is no absolute hindrance to reestablish full function. In these cases a tissue augmentation would be sufficient to give the support needed by the remaining function to function properly.

A 55 year old woman called for urine leakage in connection with physical exercise. The problem was increasing over the years. Following investigation with fiberoptic technique and ultrasonic waves it was established that the sphincter had been partially impaired. After injection of 5 ml 20% polymer lactide solution under the mucous membrane reforming a circular opening, the woman had no complications 3 months following the treatment.

Corresponding treatments of other ring muscle sphincters are appearent for the skilled man within this art.

Example 4:

Vocal cord atrophy

A special case was a patient whose voice had been nearly lost after a radiation treatment of the neck region. Following investigation, it was established that one of the vocal cords had atrophiated and been longitudinally displaced. This led to an almost wheezing voice being awkward for the patient in his working life. Under fiberoptic controll an injection in the impaired part of the vocal cord was given with 2 ml 20% of lactide polymer solution. A voice function sufficient for the patient was stabilized after 3 months.

Example 5 : Tissue augmentation combined with filling

A solution of 20 g of high molecule weight polylactide in 100 g of acetone was prepared. To the resulting highly viscous solution was added about 20 g dry dextranomer particles which allow the solution to be modulated following injection. The mixture was allowed to stabilize. After transfer to a syringe the slurry was injected into the wall of a pig bladder. Histological examination three months later revealed a localized white patch with multiple channels and fibrous tissue ligaments. There were no signs of a foreign body reaction.

Example 6 : Tissue augmentation combined with filling

Particles of l-polylactide were formed by heating a mixture of said material with a surplus of sodium bicarbonate crystals according to the procedure described in WO 92/21326 until the polylactide had melted and evenly mixed with the salt crystals. The mixture was cooled and transferred to distilled water. 5 grams of the thus obtained acetone-insoluble lactide particles were dried and mixed with a solution made from 5 grams of dl-polylactide in 100 grams of acetone. This gives a coherent slurry.

0,2 ml of that mixture was injected subcutaneously into a nude mouse. The bolus so formed was very pronounced and stayed the same throughout a 12 weeks period. This formulation shows excellent properties for soft tissue augmentation. Initially

there was an inflammatory reaction that lasted for 6 hours. At the end of the experiment, histological examination did not reveal any foreign body reaction.

Example 7 : Tissue augmentation combined with filling

To a solution of 20 grams of dl-polylactide/polyglycolide copolymer dissolved in 100 grams of acetone was added 5 grams of a microcrystalline powder mixture of equimolar amounts of citric acid and sodium bicarbonate. The resulting slurry was transferred to syringes and injected in 0.5 ml portions into the earlaps of young pigs. The next day a 2-3 ml foam had developed that felt like semi hard tissue like the cartilage itself. These properties were obtained because of the gas evolving nature of the filling material. In principle, any filling material evolving gas in an aqueous system at about 37°C can be used. Three months later the animal was sacrificed and at autopsy the foam was still very "spongy" and there were no signs of foreign body reaction.

Release test

500 mg of chlorhexidine was melted into 5 grams of l-lactide and casted to particles as described in WO 92/21326. After mixing with a solution made of 5 grams of dl-polylactide in 50 grams of acetone, the resulting fluid was tested for release of chlorhexidine in a water system. The composition released chlorhexidine for more than 30 days.

From the above it appears that the disclosed tissue augmentation obtained by injection under fiberoptic guidance is a fast, cheap and simple method probably not leading to a permanent condition but which under some years recreate a lost function. Because of the simplicity of the method the treatment can easily be repeated as needed.

CLAIMS

1. Use of a biologically degradable polymer for manufacturing of a composition for treating an impaired tissue by injecting said composition into said tissue for the purpose of joining and/or augmenting thesame, said composition being in liquid state at the time of injection and in solid state following injection.

2. Use according to claim 1, wherein the biologically degradable polymer being chosen from the group consisting of polyglycolides and copolymers thereof, polylactides and copolymeres thereof, poly-β-hydroxybutyrate and copolymeres thereof, poly-p-dioxanone, poly-δ-valerolactone, poly-ϵ-caprolactone, methylmetacrylate-N-vinyl pyrrolidone copolymeres, polyesteramides, polyesters of oxalic acid, polydihydropyranes, poly-alkyl-2-cyanoacrylates, polyurethanes, polyvinylalcohol, polypeptider, poly-β-maleic acid, poly-β-alkanoinic acids, alginates in different forms, and a combination of one or more of these.

3. Use according to claims 1 or 2, wherein said polymer is dissolved in a solvent before said injection.

4. Use according to claims 1 or 2, wherein said polymer is heated before said injection.

5. Use according to claims 1 or 2, wherein said polymer is cross linked in situ in said tissue.

6. Use according to one or more of the claims 1-5, wherein said composition also comprises a drug.

7. Use according to one or more of the claims 1-6, wherein said composition also comprises monofilaments.

8. Use according to one or more of the claims 1-7, wherein said composition also comprises tissue expanding agents.

9. Composition for tissue augmentation comprising 1-50% by weight of a biologically degradable polymer and at least 1% by weight of dextranomer particles.

10. Composition for tissue augmentation comprising 1-50% by weight of a biologically degradable polymer and at least 1% by weight of gas forming agent(s).

11. Composition according to claim 11, wherein the gas forming agents are particulate citric acid and sodium bicarbonate.

12. Composition for tissue augmentation comprising 1-50% by weight of a biologically degradable polymer and at least 1% by weight of solvent-insoluble polymer particles.

13. A method of tissue augmentation, comprising
a) insertion of an instrument into a tissue where the augmentation is desired;
b) creation of cavity(ies) in the tissue by said instrument;
c) removal of the instrument;
d) insertion of a cannula or catheter filled with a liquid composition comprising a hardenable biologically degradable polymer in the cavity (-ies), and injection of the composition therein; and
e) withdrawal of the cannula and hardening of the polymer.

14. A method according to claim 13, wherein it is performed under fiberoptic guidance.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 93/00586

A. CLASSIFICATION OF SUBJECT MATTER

IPC5: A61L 27/00
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC5: A61L

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

WPI, CLAIMS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO, A1, 9101126 (ATRIX LABORATORIES, INC.), 7 February 1991 (07.02.91), see page 6, lines 11-12, page 15, lines 5-26, claims	1-12
P,A	US, A, 5204382 (DONALD G. WALLACE ET AL), 20 April 1993 (20.04.93)	1-12
A	US, A, 4803075 (DONALD G. WALLACE ET AL), 7 February 1989 (07.02.89)	1-12

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" erlier document but published on or after the international filing date
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Date of the actual completion of the international search	Date of mailing of the international search report
27 October 1993	02 -11- 1993
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Sofia Nikolopoulou Telephone No. +46 8 782 25 00

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 93/00586

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US, A, 4595713 (KENNETH ST. JOHN), 17 June 1986 (17.06.86) --	1-12

INTERNATIONAL SEARCH REPORT

Ir. ational application No.

PCT/SE 93/00586

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 13-14
because they relate to subject matter not required to be searched by this Authority, namely:

See PCT Rule 39.1(iv): Methods for treatment of the human or animal body by surgery or therapy, as well as diagnostic methods.

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

01/10/93

International application No.
PCT/SE 93/00586

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO-A1- 9101126	07/02/91	AU-A- 6071890	22/02/91
		CA-A- 2063729	25/01/91
		EP-A- 0484387	13/05/92
US-A- 5204382	20/04/93	WO-A- 9316657	02/09/93
US-A- 4803075	07/02/89	AU-A- 7467187	07/01/88
		EP-A- 0251695	07/01/88
US-A- 4595713	17/06/86	AU-B- 578135	13/10/88
		AU-A- 5353086	13/08/86
		EP-A- 0210226	04/02/87